REMARKS

I. Status of the Application

Claims 1-3, 6, 12, 14, 15, 52-60, and 70-76 are presently pending in the application. Claims have been amended to recite removal of a protective group making the reactive functional group available for reaction with a synthesis intermediate. Support for the amendment is found at page 4 lines 10-12 of the specification.

II. Rejection of Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 Under 35 U.S.C. § 112

Claims 1-3, 6, 12, 14-15, 52-60, and 70-76 stand rejected under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention.

At page 5, paragraph 14.A. and page 7, paragraph 14.H. of the Office Action, the Examiner has rejected claims 2 and 52 as being indefinite for lacking proper antecedent basis for "protecting group" in the last line of the claim. Applicants have amended claims 2 and 52 to read, "protecting groups" to conform with the Examiners suggestion. Accordingly, Applicants respectfully request withdrawal of the rejection.

At pages 5, paragraph 14.B of the Office Action, the Examiner has rejected claim 2 for insufficient antecedent basis for "radiation sensitive compound." Applicants have amended claim 2 to read "radiation sensitive compound or group" as the Examiner requested to bring this claim into condition for allowance. Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 6, paragraph 14.C. of the Office Action, the Examiner has rejected claim 3 for insufficient antecedent basis for "autocatalytic compound." Applicants have amended claim 3 to read "autocatalytic compound or group," as the Examiner suggested. As a result, Applicants respectfully request withdrawal of the rejection.

At page 6, paragraph 14.D. of the Office Action, the Examiner has rejected claim 12 for insufficient antecedent basis for "photosensitive compound." Applicants have amended claim 12 to depend from claim 2. For that reason, Applicants respectfully request withdrawal of the rejection.

At page 6, paragraph 14.E. of the Office Action, the Examiner has rejected claim 14 for insufficient antecedent basis for the term "removable protecting group." Applicants have

amended claim 14 to read "protecting group" and argue that there is proper antecedent basis for "protecting group" in line 7 of claim 1.

At page 7, paragraph 14.F - G. of the Office Action, the Examiner has rejected claim 15 for insufficient antecedent basis for the terms "photosensitive group" and "autocatalytic group." Applicants have amended claim 15 to depend from claim 2. For that reason, Applicants respectfully request withdrawal of the rejection.

At page 8, paragraph 14.I. of the Office Action, the Examiner has rejected claim 53 for insufficient antecedent basis for the term "photosensitive compound or group." Applicants have amended claim 53 to read "photosensitive acid compound or group" as the Examiner suggested to give the term proper antecedent basis. Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 8, paragraph 14.J. of the Office Action, the Examiner has rejected claim 54 for insufficient antecedent basis for the term "autocatalytic compound." Applicants have amended claim 54 to read "autocatalytic compound or group" in line with the Examiner's suggestion. Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 8, paragraph 14.K. of the Office Action, the Examiner has rejected claim 57 for insufficient antecedent basis for the term "removable protecting group." Applicants have amended the claim to read "protecting group." Proper antecedent basis for "protecting group" can be found in the preamble claim 52. Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 8, paragraph 14.L. of the Office Action, the Examiner has rejected claim 58 for insufficient antecedent basis for the term "photosensitive compound." Applicants have amended claim 58 to read "photosensitive acid compound or group" to overcome the rejection, as the Examiner suggested. Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 9, paragraph 14.M. of the Office Action, the Examiner has rejected claim 71 for insufficient antecedent basis for the term "photosensitive compound or group." Applicants have amended claim 71 to read "photosensitive acid compound or group" in order to overcome the rejection. Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 9, paragraph 14.N. of the Office Action, the Examiner has rejected claim 74 for insufficient antecedent basis for the term "photosensitive compound." In response, Applicants

have amended claim 74 according to the Examiner's suggestion to read "photosensitive acid compound or group." Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 9, paragraph 14.O. of the Office Action, the Examiner has rejected claims 14 and 57 for reciting the indefinite and/or unclear phrase "removable protecting group." Applicants have amended claims 14 and 57 to recite only "protecting group." Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 10, paragraph 14.P. of the Office Action, the Examiner has rejected claims 3 and 54 for recitation of the indefinite and/or unclear phrase "masked acid." Applicants would like to point out that support for the phrase "masked acid" can be found at least on page 20, lines 28 – 31 of the application. Accordingly, Applicants respectfully request withdrawal of the rejection.

At page 10, paragraph 14.Q. of the Office Action, the Examiner has rejected claims 1, 52, and 70 for reciting the indefinite and/or unclear phrase "forming a surface." Applicants assert that the specification contains sufficient support for the phrase "forming a surface." Support can be found in Example II at page 29, lines 12 – 15. Specifically, "A poly(ethylene glycol) linker molecule containing a DMT protected hydroxyl group was covalently bound to a substrate. The **surface** of the substrate **was then coated** with polymer...." It is clear from this example that "forming a surface" is implicitly occurring when the linker is being bound to the surface of the substrate. Additional support is found in Example III at page 31, lines 8 – 11 of the application. The relevant portion reads, "The coated substrate was prebaked at 85°C for 2 min, irradiated with varying doses at 365 nm, and postbaked at 85° C for 2 min. The polymer coating was then removed with an acetone wash and the **surface** treated with a fluorescent coupling reagent." In this example, it is implicitly clear that a surface is being formed by the processes of prebaking, irradiating, postbaking, removing the polymer coating, and then treating with a fluorescent coupling agent. Applicants respectfully request withdrawal of the rejection.

III. Claims 1, 2, 6, 12, 15, 52, 53, 55-57, and 70-73 Are Nonobvious Over Holmes in View of Holmes

At page 11, paragraph 15 of the Office Action, the Examiner has rejected claims 1, 2, 6, 12, 15, 52, 53, 55-57, and 70-73 under 35 U.S.C § 102(b) as being anticipated by Holmes, U.S. Pat. No. 5,242,974 ("the '974 patent") in view of Holmes, U. S. Pat. No. 5,679,773 ("the '773 patent"). Although the rejection based on the two Holmes references is identified as being under

§ 102(b), applicants respectfully believe this citation to be in error as the substance and meaning of the Examiner's rejection seems to be one of obviousness. Accordingly, applicants are responding to the rejection as if it is one under § 103.

The Examiner asserts that the Holmes '974 patent teaches methods for the removal of protecting groups in solid-phase synthesis and that the protecting group can be removed from a "synthetic intermediate" on a "surface." The Examiner then asserts that the '773 patent discloses a "photolabile" NVOC protecting group which can act as a "radiation sensitive compound," a "catalyst," and an "autocatalytic compound." Finally, the Examiner asserts that the '974 patent teaches "light-directed, spatially-addressable techniques" for removing protecting groups.

Applicants respectfully traverse the rejection. As amended, Applicants' claims are directed to a method of removing a protecting group from a reactive functional group to make the reactive functional group available for reaction with a synthesis intermediate. The Examiners primary reference, the Holmes '974 patent, fails to teach or suggest the removal of a protecting group from a reactive functional group to make the reactive functional group available for reaction with a synthesis intermediate or the use of an autocatalytic group to remove a protecting group. Instead, the Holmes '974 patent teaches a method for cyclization and reversal of the polarity of polymers on a substrate.

The Holmes '773 patent teaches linking groups useful in solid phase synthesis. The Holmes '773 patent does not teach or suggest the forming of a surface using an autocatalytic compound. Applicants submit that the Holmes '773 patent does not fairly teach at col. 18, lines 43 – 54 that NVOC is a radiation sensitive compound and a catalyst. In fact, the Holmes '773 patent teaches that the 6,6-azo-bisveratiric acid produced upon light activation of the NVOC group is undesirable and they provide procedures for removal of the species. In addition, there is no motivation to combine or to modify the Holmes '974 patent with the Holmes '773 patent in the manner suggested by the Examiner because the Holmes '773 patent teaches the undesirability and removal of the NVOC species. Accordingly, the Holmes '773 patent fails to cure the deficiency of the Holmes '974 reference.

Thus, the combination of the two Holmes references do not teach or suggest applicants' invention, and applicants respectfully request withdrawal of the obviousness rejection.

IV. Claims 1, 2, 6, 12, 15, 52, 53, 55-57, and 70-73 Are Novel Over MacDonald et al.

At page 16, paragraph 16 of the present Office Action, claims 1, 2, 6, 12, 15, 52, 53, 55-57, and 70-73 stand rejected under 35 U.S.C. § 102(b) as being anticipated by MacDonald et al (ACC. Chem. Res. 27(6):151(1994)). The Examiner asserts that MacDonald et al teach the removal of the t-BOC protecting groups. The Examiner also asserts that MacDonald et al teach that the protecting group can be removed from a "synthetic intermediate" on a "surface." In addition, the Examiner asserts that MacDonald discloses triphenylsulfonium hexafluoroantimonate, a light activated catalyst that when activated can cleave the t-BOC protecting group and cleave more triphenylsulfonium hexafluoroantimonate. Finally, the Examiner asserts that MacDonald et al teach "light-directed, spatially-addressable techniques" for removing protecting groups. Applicants respectfully traverse the rejection.

MacDonald is directed to a photolithographic process and fails to teach the limitation of making a reactive functional group available for reaction with a synthesis intermediate. MacDonald, in fact, teaches the removal of the entire "surface" of a polymeric photoresist layer when it is exposed to UV light. There is no teaching or suggestion in MacDonald that any reactive functional group is present on the substrate surface when the resist layer is removed. This is in direct contrast to the method taught in the instant application, wherein a protecting group is removed to reveal a reactive functional group for later reaction with a synthesis intermediate or other compound. For example, see page 152, second column, where "reducing the resist film thickness in the exposed areas..." is taught.

Thus, MacDonald fails to teach all of Applicant's claim limitations. According, Applicant respectfully requests that the Examiner withdraw the obviousness rejection.

Respectfully submitted,

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Version of Amendments With Markings to Show Changes Made

1. (Twice Amended) A method for removing a [protective] protecting group from a [synthesis intermediate] reactive functional group comprising the steps of:

a) forming a surface comprising

i) a radiation sensitive compound or group, said radiation sensitive compound or group producing a catalyst when irradiated, and

ii) an autocatalytic compound or group, said autocatalytic compound or group generating a protecting group removing product when said autocatalytic compound is activated by said catalyst; and

b) irradiating at least a part of said surface to remove said protecting group making the reactive functional group available for reaction with a synthesis intermediate or other compound.

2. (Twice Amended) The method recited in claim 1 wherein said radiation sensitive compound or group is a photosensitive compound or group.

3. (Twice Amended) The method recited in claim 1 wherein said autocatalytic compound or group is a member selected from the group consisting of a masked acid and pentafluorobenzoic acid.

12. (Amended) The method recited in claim [1] 2 wherein said photosensitive compound or group is a member selected from the group consisting of a photoactivated catalyst, a photoactivated acid catalyst and toluenesulfonic acid.

14. (Amended) The method recited in claim 1 wherein said [removable] protecting group is 5' dimethoxytrityl.

15. (Amended) The method recited in claim [1] 2 wherein said photosensitive compound or group and said autocatalytic compound or group are parts of the same compound.

52. (Amended) A method for removing a [protective] protecting group from a [synthesis intermediate] reactive functional group comprising the steps of:

a) forming a surface comprising

i) a photosensitive acid compound or group, the photosensitive acid, compound, or group producing a catalyst when irradiated, and

ii) an autocatalytic compound or group, the autocatalytic compound or group generating a protecting group removing product when the autocatalytic compound or group is activated by said catalyst; and

b) irradiating at least a part of said surface to remove the protecting group making the reactive functional group available for reaction with a synthesis intermediate.

53. (Amended) The method of claim 52 wherein the photosensitive acid, compound, or group is a photoactivated acid catalyst.

54. (Amended) The method of claim 52 wherein the autocatalytic compound or group is a member selected from the group consisting of a masked acid and pentafluorobenzoic acid.

58. (Amended) The method of claim 52 wherein the [removable] protecting group is an acid removable group.

59. (Amended) The method of claim 52 wherein the photosensitive acid, compound, or group is toluenesulfonic acid.

60. (Amended) The method of claim 52 wherein the protecting group is selected from the group consisting of dimethoxytrityl, tert-butylcarbamate, trifluoroacetyl, 9-fluorenylmethoxycarbonyl, isobutyrl, benzoyl, phenoxyacetyl, acetamidomethyl, acetyl, tert-amyloxycarbonyl, benzyl, benzyloxycarbonyl, 2-(4-biphenylyl)-2-propyloxycarbonyl, 2-bromobenzyloxycarbonyl, tert-butyl, tert-butyloxycarbonyl, 1-carbobenzoxamido-2,2,2-trifluoroethyl, 2,6-dichlorobenzyl, 2-(3,5-dimethoxyphenyl)-2-propyloxycarbonyl, 2,4-dinitrophenyl, dithiasuccinyl, formyl, 4-methoxybenzenesulfonyl, 4-methoxybenzyl, 4-

methylbenzyl, [o-nitrophenylsulfenyl] o-nitrophenylsulfonyl, 2-phenyl-2-propyloxycarbonyl, alpha.-2,4,5-tetramethylbenzyloxycarbonyl, p-toluenesulfonyl, xanthenyl, benzyl ester, N-hydroxysuccinimide ester, p-nitrobenzyl ester, p-nitrophenyl ester, phenyl ester, p-nitrocarbonate, p-nitrobenzylcarbonate, trimethylsilyl and pentachlorophenyl ester.

70. (Amended) A method for removing a protecting group from a [synthesis intermediate] reactive functional group comprising the steps of:

a) forming a surface comprising

i) a synthesis intermediate having an acid removable protecting group, and

ii) a photosensitive acid, compound, or group, the photosensitive acid, compound, or group producing an acid when irradiated, and

b) irradiating at least a part of the surface with light to generate an acid and to remove the acid removable protecting group making the reactive functional group available for reaction with a synthesis intermediate or other compound.

71. (Amended) The method of claim 70 wherein the photosensitive acid, compound, or group is a photoactivated acid catalyst.

74. (Amended) The method of claim 70 wherein the photosensitive acid, compound, or group is toluenesulfonic acid.

Each of the above techniques produces only a relatively low density array of polymers. For example, the technique discussed in Geysen et al. is limited to producing 96 different polymers on pins spaced in the dimensions of a standard microliter plate.

SUMMARY OF THE INVENTION

Improved methods of forming high density arrays of peptides, polynucleotides, and other polymer sequences in a short period of time have been devised using combinatorial solid phase synthesis. Very Large Scale Immobilized Polymer Synthesis (VLSIPS) technology has greatly advanced combinatorial solid phase polymer synthesis and paved the way to clinical application of deoxyribonucleic acid (DNA) array chips such as those sold under the trademark GENECHIP. See Kozal et al., *Nature Medicine*, Vol. 2, pp. 753-759 (1996), incorporated herein by reference in its entirety for all purposes. VLSIPS technology is disclosed in Pirrung et al., U.S. Patent No. 5,143,854 (see also PCT Publication No. WO 90/15070), Fodor et al., PCT Publication No. WO 92/10092, and PCT Publication No. WO 95/11995; Fodor et al.., *Science* (1991) 251:767-777, all incorporated herein by reference in their entirety for all purposes. Known embodiments of VLSIPS technology employ radiation-labile protecting groups and photolithographic masks to achieve spatially defined combinatorial polymer synthesis on a substrate surface. In those embodiments, masks are used to control the selective exposure to radiation in specific locations of a surface provided with linker molecules containing radiation-labile protecting groups. In the exposed locations, the radiation-labile protecting groups are removed. The surface is then contacted with a solution containing a desired monomer. The monomer has at least one site that is reactive with the newly exposed reactive moiety on the linker and at least a second reactive site protected by one or more radiation-labile protecting groups. The desired monomer is then coupled to the unprotected linker molecules. The process can be repeated to synthesize a large number of polymer sequences in specific locations.

Other methods for synthesizing high density polymer arrays employ blocks containing channels for reagent delivery at preselected sites on the substrate. See PCT Publication No. WO 93/09668, incorporated herein by reference for all purposes. In certain embodiments, a block is contacted with the substrate and the reagents necessary to form a portion of the immobilized polymer are permitted to access the substrate via the channel(s). The block or substrate can be rotated and the process repeated to form arrays

of polymers on the substrate. The block channel method can be combined with light-directed methodologies.

Certain embodiments of the present invention provide novel methods, compositions, and devices useful in synthesizing novel high density arrays of diverse polymer sequences. The polymer sequences are fashioned from individual synthesis intermediates and include diverse naturally or non-naturally occurring peptides, nucleotides, polypeptides or polynucleotides. The methods of the present invention utilize a novel chemical amplification process using a catalyst system which is initiated by radiation to assist in the synthesis the polymer sequences. Methods of the present invention include the use of photosensitive compounds which act as catalysts to chemically alter the synthesis intermediates in a manner to promote formation of polymer sequences. Such photosensitive compounds include what are generally refered to as radiation-activated catalysts (RACs), and more specifically photo activated catalysts (PACs). The RACs can by themselves chemically alter the synthesis intermediate or they can activate an autocatalytic compound which chemically alters the synthesis intermediate in a manner to allow the synthesis intermediate to chemically combine with a later added synthesis intermediate or other compound.

According to one embodiment of the present invention, one or more linker molecules are bound to or otherwise provided on the surface of a substrate, such as a glass plate. The unbound portion of the linker molecule, also referred to as the terminal or free end of the linker molecule, has a reactive functional group which is blocked, protected or otherwise made unavailable for reaction by a removable protective group. Once the protective group is removed, the functional group is made available for reaction, i.e. the reactive functional group is unblocked. A photo activated catalyst (PAC) is also located or otherwise provided on the surface of the substrate in the vacinity of the linker molecules. An autocatalytic compound may also be present on the surface of the substrate. The photo activated catalyst by itself or in combination with additional catalytic components is referred to herein as a catalyst system.

Using lithographic methods and techniques well known to those of skill in the art, a set of first selected regions on the surface of the substrate is exposed to radiation of certain wavelengths. The radiation activates the PAC which then either directly or through an autocatalytic compound catalytically removes the protecting group from the